

REMARKS/ARGUMENTS

The aforementioned amendments to claims 1, 3, 11, 12, 13, 14, and 15 are respectfully submitted in response to the official action dated August 6, 2008. In light of these amendments and the following remarks, it is once again respectfully submitted that all of the claims in this application are now clearly directed to patentable subject matter, and that they overcome the rejections set forth in the latest official action herein. For this reason alone, it is believed that good cause has been shown for the entry of these amendments. In addition, they clearly reduce the number of issues presented for purposes of appeal. Thus, entry of these claims is believed to be appropriate, and in any event, reconsideration and allowance of these claims is respectfully solicited.

The amendments to claim 1 incorporate the limitations with respect to the weight percent of the active ingredient which were previously set forth in claim 16, now canceled. Thus, this limitation is clearly supported, as was previously the case. The further amendments to claim 1 limiting the active ingredient to albuterol are specifically supported in the specification such as at page 6, paragraph [0027], line 4 and page 12, paragraph [0050], line 3, for example. It is thus clear that no new matter is included in these amendments, and their entry is therefore respectfully solicited.

Claims 1, 2, 5, 6, and 8-10 have been rejected as being anticipated by Haeberlin under 35 U.S.C. § 102(b). The Examiner contends that Haeberlin discloses dry powder formulations particularly effective for treating COPD when administered as a dry powder comprising formoterol in admixture with a diluent or carrier in an amount of 400 to 5,000 micrograms per microgram of formoterol active, and that a

composition comprising 400 micrograms of diluent and 1 microgram of formoterol active comprises 0.25% w/w active. Suitable diluents or carriers are said to include lactose, and the mean particle diameter of the formoterol active is said to preferably be up to 10 microns, particularly 1-5 microns. The diluent or carrier is said to have a maximum diameter of 300 microns and preferably 212 microns, and in a preferred embodiment the dry powder is said to be in a capsule with a unit dose of the active in which the diluent or carrier is preferably such that the total weight of the dry powder per capsule is between 5 and 25 mg. Doses of formoterol active are said to be from 1 to 60 micrograms, and in another embodiment the dry powder is said to be in a reservoir or multidose dry powder inhaler adapted to deliver a unit dose. These inhalers are said to be well known and commercially available and gelatin capsules containing dry powder compositions comprising formoterol fumarate dihydrate in admixture with lactose monohydrate are said to be exemplified in Examples 1-29. Example 6 is said to disclose a composition in which the formoterol active is present in amounts of 0.24% w/w.

In response to applicant's arguments, the Examiner disagrees with applicant's prior citation of the *Atofina* case and again states that when fairly comparing calculated numerical values it is said to be imperative that one utilize the same number of significant figures. Thus, since applicant's claimed minimum is recited only in two significant figures, it is said to be inappropriate to calculate the prior art at three significant figures. When this is done, the prior art value is said to touch applicant's claimed range. As for *Atofina*, the facts are said not to be dispositive because this case discusses a broad prior art range encompassing a much smaller claimed range where the prior art range did not touch any point of the claimed range, as opposed to the present situation in which a single point does touch the claimed range. This rejection is

respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

It is, of course, initially noted that all of the claims in this application are now specifically directed to the active ingredient albuterol. Albuterol, on the other hand, is not suggested, referred to, or even mentioned in Haeberlin. Indeed, that patent is specifically and solely directed to alleged surprising results found in connection with the use of formoterol or pharmaceutically acceptable salts or solvates thereof. For this reason alone, the claims clearly cannot be said to be anticipated by Haeberlin. Secondly, however, all of the claims now specifically require that, even with albuterol, this active be present in amounts of greater than 0.26% w/w. Thus, at either two or three significant figures, and irrespective of applicant's position in this regard, there is no teaching in Haeberlin of using the amounts of the particular active (namely, albuterol), or any active, including the formoterol in Haeberlin itself, in the amounts required by all of the present claims. It is therefore now clear beyond question that a rejection of these claims based on alleged anticipation is no longer appropriate and should be withdrawn.

Indeed, it is now also quite clear that any attempt to stretch the Haeberlin reference to anticipate these claims is not legally appropriate. Once again, in *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991 (Fed. Cir. 2006), the Federal Circuit reversed a similar attempt to create an anticipatory reference. In *Atofina* the district court had found anticipation of (1) a claimed temperature range of 330°C to 450°C in a reference disclosing a corresponding temperature range of 100°C to 500°C, and a preferred temperature range of 150°C to 350°C; and (2) a claimed oxygen to methylene molar ratio of 0.1% to 5.0% in a reference disclosing a corresponding oxygen to methylene molar ratio of 0.001 to 1.0%. In reversing, the Federal Circuit

stated that "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this limitation of the claim." (*Id.* at 999.) The court went on to analyze the contention that the reference anticipated the temperature range because the preferred range slightly overlapped the claimed range. Here the court stated:

But that slightly overlapping range is not disclosed as such, i.e., as a species of the claimed generic range of 330 to 450°C. Moreover, the disclosure of a range of 150 to 350°C does not constitute a specific disclosure of the endpoints of that range, i.e., 150°C to 350°C The disclosure is only that of a range, not a specific temperature in that range, and the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points. Thus, [the reference] does not disclose a specific embodiment of the claimed temperature range

Id. at 1000.

A similar conclusion was reached with respect to the oxygen to methylene molar ratios. In all respects, Haeberlin clearly does not anticipate the claims pending in this application, and withdrawal of this rejection is therefore respectfully solicited. Furthermore, it is certainly clear at this point that these claims do not overlap with the disclosure in Haeberlin. Indeed, since the Examiner has not rejected claims such as claim 3 on the basis of Haeberlin in this rejection, it is clear that this rejection is no longer applicable to the amended claims herein.

Claims 1-6 and 8-16 have been rejected as being unpatentable over Haeberlin under 35 U.S.C. § 103(a). In addition to the Examiner's comments with respect to Haeberlin, with respect to prior claim 4, the claims were said to comprise about 0.26% to about 1% w/w active and the term "about" is said

to be defined to mean a variance of 5% of both the upper and lower limits of stated values. The Examiner concludes that it would be obvious to optimize the amounts of formoterol in the compositions of Haeberlin based on the needs of subjects in need of administration of formoterol. The ratio of formoterol to diluent/carrier disclosed in Haeberlin is said to be particularly effective for treating COPD, and this description is said not to constitute a teaching away from compositions with greater amounts of formoterol. The amount of specific ingredients is said to clearly be a result of effective parameters that one would routinely optimize. Thus, absent some demonstration of unexpected results for the claimed parameters, optimization was said to be obvious at the time of the invention. In response to applicant's arguments, the Examiner further contends that it would be well within the capability of ordinary skilled artisans to adjust the amount of active based upon the subjects needs, and that such modification is an obvious way to increase the amount of active administered. Applicant has been said not to have demonstrated any particular criticality regarding the amount of active present in the claimed compositions and is said not to have asserted that amounts greater than 0.25% yield unexpected or surprising results or that compositions comprising amounts below 0.25% exhibit undesirable properties. General statements by applicant are said not to be persuasive. Applicant is said not to have provided any probative comparative evidence as to the implied surprising properties of greater accurate dosing and uniformity and consistency. This rejection is respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

It is, of course, initially noted that in view of the above amendments the fact is that the Haeberlin reference now not only does not teach the use of the specific formulation and

amounts of active set forth in the claims, but that Haeberlin does not teach the specific active to which the present claims are now directed, in any formulations, and certainly not in the claimed formulations hereof. The issue again becomes whether or not a *prima facie* case of obviousness has been made out by the Examiner. It is once again submitted that an overall review of the Examiner's position reveals that it does amount to a general contention that any ratio with any common or similar drug, would be obvious. This is submitted, however, not to meet the requirements of the appropriate burden of proof.

As described in the specification in connection with these types of TPI devices, the drug particles are blended with an excipient to create a generally homogeneous mixture. The larger particle size of the excipient results in the powder mixture being flowable and the homogeneity of the mixture enables it to be metered into accurately measurable dosages. This is said to be of particular importance when only very small quantities of drug are required in a dose. With the use of greater percentages of active ingredient than those disclosed in the prior art, applicant has demonstrated in the examples that he was able to achieve excellent dose uniformity irrespective of this fact. This, of course, is a critical factor in connection with such multidose inhalers and is not suggested by the Haeberlin reference. In Example 2, for example, the results demonstrate an extremely efficient and reproducible blending and handling process with compositions giving excellent dose uniformity. There is also no difference in the fine particle fraction of formoterol between the 6 mcg and 12 mcg strength products, indicating consistent performance of these products. None of this is suggested in the Haeberlin reference. Indeed, the Examiner can take judicial notice of the fact that conventional thinking of those of ordinary skill in this art would be that more dilute formulations would generally be

expected to provide better uniformity, and *vice versa*. Thus, these experts would clearly expect that the lower the percentage of active ingredient, such as albuterol, the larger the sample of such medicament which would be required to deliver the same amount of the specified active ingredient to the patient. As the sample thus becomes larger, so it would be far more likely to be representative of the overall batch from which it was produced. Thus, it would be far more likely to be uniform as compared to other doses. It is thus clearly expected that in the case of utilizing higher percentages of the selected active ingredient, such as in connection with the present invention, the smaller the sample of the medicament required to deliver the same amount of this active. This, in turn, would be expected to result in a concomitant reduction in the uniformity of each dose thereof. Applicant has quite unexpectedly discovered, however, that contrary to this logically expected result, he is nevertheless able to increase the percentage of the selected active ingredient without experiencing the expected adverse effect on uniformity.

Therefore, the blanket statement that one of ordinary skill in this art would be able to place any amount of active in the composition and expect to get results, particularly in the face of a reference which not only fails to teach the amounts of active required by the present claims, but specifically states that the amounts set forth in Haeberlin were "particularly effective," cannot in applicant's view be taken as a teaching or suggestion to utilize the far different amounts claimed herein. As applicant has also previously asserted, persons skilled in this art would not have even further "optimized" the amount of formoterol based on Haeberlin, much less the presently claimed albuterol, to produce a composition in which that amount is outside the range disclosed by Haeberlin. Furthermore, "[a] particular parameter must first be recognized as a result-

effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable range of said variable might be characterized as routine experimentation." M.P.E.P. (8th ed, Rev. 5, August 2006), at 2100-71 (citing *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977)).

Applicant has convincingly demonstrated that the presently claimed dry powder formulations are more accurately metered and provide more uniform and consistent dispersions when dispensed by MDPI devices. Such dry powder formulations would not have been produced by optimization based on patient needs. Patient needs determine the amounts of drug delivered to a patient which may be varied by varying the quantity of the dry powder formulation delivered without varying the proportion of the drug in the formulation as in accordance with the present invention.

It is therefore respectfully submitted that all of the claims in this application now possess the requisite novelty, utility of unobviousness to warrant their immediate allowance, and such action is therefore respectfully solicited.

Claims 1, 4-7, and 9 have been rejected on the basis of obviousness-type double patenting over claims 1 and 9-11 of co-pending Application No. 10/646,361 in view of Haeberlin. Applicant again respectfully requests, however, that this obviousness-type double-patenting rejection be held in abeyance until the prosecution of this application has been completed.

Applicant again respectfully requests that the Examiner reconsider these rejections and allow the present claims in their present form. If, however, for any reason the Examiner does not believe that such action can be taken, it is respectfully requested that he telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

Finally, if there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: February 5, 2009

Respectfully submitted,

By 

Arnold H. Krumholz

Registration No.: 25,428

LERNER, DAVID, LITTENBERG,

KRUMHOLZ & MENTLIK, LLP

600 South Avenue West

Westfield, New Jersey 07090

(908) 654-5000

Attorney for Applicant

\975036_1.DOC